Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 36-37 and 39-42 are pending in the application, with claims 36 and 42 being the independent claims. Claims 36 and 42 have been amended to clarify the antecedent basis of "candidate agent." These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Response to Amendment

Applicants thank the Examiner for reconsidering and withdrawing the prior rejection of the claims.

Rejection under 35 U.S.C. § 112, second paragraph - definiteness

The Examiner rejected claims 36-37 and 39-42 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. *See* Office Action at pages 3-4. In particular, the Examiner alleges that there is insufficient antecedent basis in claims 36 and 42 for the "candidate agent" in steps (d) and (g), because the preamble reads "an agent." *See* Office Action at page 3. Claims 37 and 39-41 are rejected as depending from rejected claims 36 and 42. *See* Office Action at page 4.

Solely to advance prosecution, and not in acquiescence to the Examiner's rejection, Applicants have amended claims 36 and 42 to clarify that the antecedent basis of "candidate agent." Therefore, Applicants submit that claims 36-37 and 39-42 have proper antecedent basis and respectfully request that this rejection be reconsidered and withdrawn.

Rejections under 35 U.S.C. § 103

The Examiner rejected claims 36, 39 and 40-41 as allegedly obvious over Dyrks *et al.* (J. Biol. Chem. 267:18210-18217, 1992), in view of Bush *et al.* (Science 265: 1464-1467, 1994) and Mantyh *et al.* (J. Neurochem. 61:1171-1174, 1993). *See* Office Action at pages 4-8. Applicants respectfully traverse.

The Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the cited art. *See In re Piasecki*, 745 F.2d 1468, 1471-72 (Fed. Cir. 1984). The factors to be considered under 35 U.S.C. § 103(a), are the scope and content of the prior art; the differences between the prior art and the claims at issue; and the level of ordinary skill in the pertinent art. *See Graham v. John Deere*, 86 S.Ct. 684 (1966) and M.P.E.P. § 2141. This analysis has been the standard for 40 years, and remains the law today. *See KSR International Co v. Teleflex Inc.*, 127 S.Ct. 1727 (2007).

To establish a *prima facie* case of obviousness it is not sufficient to merely combine individual elements known in the prior art if the results would not have been predictable to one of ordinary skill in the art. *See Examination Guidelines for Determining Obviousness under 35 U.S.C. 103 in view of the Supreme Court decision in KSR International v. Teleflex Inc. Fed.* Reg. Vol. 72, pp. 57526 to 57535 (October 10,

2007), at page 57529. The analysis supporting a rejection under 35 U.S.C. § 103(a) should be made explicitly and "identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements" in the manner claimed. *See KSR International Co v. Teleflex Inc.*, 127 S.Ct. 1727 (2007) *citing In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements, instead, there must be some articulated reasoning with some rational underpinning to support a legal conclusion of obviousness").

At page 5 of the Office Action, the Examiner alleges that Dyrks *et al.* teaches that $FeCl_2$ causes aggregation of Aβ and A4CT, and that radical scavengers such as ascorbic acid inhibit hemoglobin- or $FeCl_2$-induced aggregation of A4CT. However, the Examiner concedes that Dyrks *et al.* does not "teach the inhibition of the aggregation of βA4 or Aβ peptide." Office Action at page 5. The Examiner further alleges that Bush *et al.* teaches that Zn^{2+} causes aggregation of Aβ, while EDTA does not cause any distinguishable Aβ aggregation. *See* Office Action at page 6. However, the Examiner concedes that Bush *et al.* does not "teach the incubation of the second Aβ sample with a metal, and an agent that inhibits the metal induced aggregation of Aβ peptide." Office Action at page 6. Finally, the Examiner alleges that Mantyh *et al.* teaches that metal ions such as Fe^{3+} cause aggregation of Aβ, and that iron-induced aggregation of Aβ is significantly higher than control values in the absence of metal ions. *See* Office Action at page 6.

One of ordinary skill in the art would not have been motivated to combine the teachings of Dyrks et al. regarding A4CT to the teachings of Bush et al. or Mantyh et al. regarding Aβ, because A4CT and Aβ have different oxidative properties.

At pages 6-7 of the Office Action, the Examiner alleges that it would have been obvious to the person of ordinary skill in the art to modify the method of Dyrks *et al.* regarding inhibition of $FeCl_2$-induced A4CT crosslinking with agents such as ascorbic acid (as taught by Dyrks *et al.*) for the identification of an agent that inhibits metal-induced aggregation of Aβ peptide (as taught by Bush *et al.* or Mantyh *et al.)*. *See* Office Action at pages 6-7. The Examiner alleges that one of ordinary skill in the art would have been motivated to do so because: (1) Aβ isoforms are implicated in the plaque formation in disease states; (2) aggregation of Aβ by metal ions contribute an early step in amyloidogenesis; (3) several amino acid residues in Aβ are capable of interaction with metal ions; (4) metal-mediated reactions lead to insoluble amyloid protein aggregates involved in the pathology leading to Alzheimer's disease; and (5) methods of inhibiting the formation of metal-induced aggregates were well known. *See* Office Action at page 7. Applicants respectfully disagree.

Applicants refer to the Declaration Under 37 C.F.R. § 1.132 by Kevin J. Barnham, Ph.D. submitted with Applicants' Amendment and Reply Under 37 C.F.R. § 1.111 filed on October 10, 2006. In his Declaration, Dr. Barnham indicates that A4CT and Aβ have different chemical natures which likely give rise to differing arrays of oxidatively modified products when subjected to metal catalyzed oxidation. *See, e.g.,* Barnham Declaration at paragraphs 15-16. Given the differing arrays of oxidatively modified products likely to be generated by metal catalyzed oxidation of A4CT and Aβ, Dr. Barnham indicates that different oxidation modifications are likely responsible for

the observed hemoglobin- and H_2O_2-induced aggregation of A4CT and Aβ in Dyrks *et al.* *See* Barnham Declaration at paragraph 17. Based on these differences, Dr. Barnham concludes that Dyrks *et al.* does not describe the method of the present claims which involves the addition of an agent capable of inhibiting redox-reactive metal-mediated crosslinking of Aβ, or create a reasonable expectation of success for the method of the present claims. *See* Barnham Declaration at paragraph 19.

In view of Dr. Barnham's Declaration, one of ordinary skill in the art would not be motivated to combine the teachings of Dyrks *et al.* related to A4CT with the teachings of Bush *et al.* or Mantyh *et al.* related to Aβ because A4CT and Aβ have different oxidative properties. Consequently, a *prima facie* case of obviousness has not been established because there is no motivation to combine the references to arrive at the present claims.

The references cited by the Examiner do not teach or suggest screening or identifying methods, or a candidate agent that inhibits redox-reactive metal-mediated crosslinking of Aβ.

The above notwithstanding, Applicants respectfully remind the Examiner that the present claims are directed to *methods* for the identification of a *candidate agent* that inhibits redox-reactive metal-mediated crosslinking of Aβ. Thus, both *methods* and *candidate agents* are basic elements of the claims. Although the references cited by the Examiner describe general observations relating to the underlying biology of A4CT and Aβ, none of the references teach or suggest the use of *candidate agents* to inhibit Aβ crosslinking. Furthermore, none of the references teach or suggest the identification of a candidate agent using *methods* that employ the criteria defined by Applicants' claims. *See, e.g.*, steps (a)-(g) of claim 42. In fact, no screening or identifying methods are

taught or suggested at all. Therefore, a *prima facie* case of obviousness cannot be established because none of the references cited by the Examiner teach or suggest two basic elements of Applicants' claims: (1) *methods* for the identification of candidate agents; and (2) a *candidate agent* that inhibits redox-reactive metal-mediated crosslinking of Aβ. Thus, for at least the above reasons, the rejection of claims 36, 39 and 40-41 under 35 U.S.C. § 103(a) should be withdrawn.

The Examiner also rejected claims 36-37 and 39-42 as allegedly obvious over Dyrks *et al.* in view of Bush *et al.* and Mantyh *et al.* *See* Office Action at pages 8-9. In particular, the Examiner alleges that Dyrks *et al.* teaches that the insoluble aggregates of Aβ are generated by metal-catalyzed crosslinking, and that A4CT aggregates generated by metal catalyzed crosslinking are causes for amyloid plaques in AD. *See* Office Action at pages 8-9. However, the Examiner concedes that none of the cited references teach the analysis of Aβ aggregates by Western blot. *See* Office Action at page 9. As such, the Examiner alleges that it would have been obvious to one of ordinary skill in the art to look for Aβ crosslinking by Western blot.

Applicants respectfully disagree. As detailed above, one of ordinary skill in the art would not be motivated to combine the teachings of Dyrks *et al.* related to A4CT to the teachings of Bush *et al.* or Mantyh *et al.* related to Aβ because A4CT and Aβ have different oxidative properties. Consequently, a *prima facie* case of obviousness has not been established because there is no motivation to combine the references to arrive at the present claims. Furthermore, Applicants submit that none of the references cited by the Examiner teach or suggest *methods* for the identification of candidate agents, or a *candidate agent* that inhibits redox-reactive metal-mediated crosslinking of Aβ. Thus,

for at least the above reasons, the rejection of claims 36-37 and 39-42 under 35 U.S.C. § 103(a) should be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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